Fruit and vegetables

No. 2021/41Be, The Hague, November 16, 2021

Background document to:
Dutch dietary guidelines for people with type 2 diabetes
No. 2021/41e, The Hague, November 16, 2021

Health Council of the Netherlands

contents

01 introduction

The current background document belongs to the advisory report *Dutch dietary guidelines for people with type 2 diabetes*.[1] It describes the methodology for the search, selection and evaluation of the literature regarding the relationship of fruit and vegetable consumption with health outcomes in people with type 2 diabetes. It furthermore describes the scientific evidence on this topic and the conclusions that have been drawn by the Health Council's Committee on Nutrition.

1.1 Definition of fruit and vegetables

Fruit

Fruit is the collective name for edible fruits. The Committee followed the definition of fruit that was applied for the *Dutch dietary guidelines 2015*.[2] In those guidelines, the definition from the European Prospective Investigation into Cancer and Nutrition (EPIC) study was used, which was based on nutrient value, taste and culinary application of plant foods.[3] The following categories of plant foods are considered fruit (list is not exhaustive):

- Citrus fruits: grapefruit, orange, tangerine, lemon;
- Non-citrus fruits: apple, pear, grape, apricot, cherry, peach, (dried) plum, nectarine, melon, pineapple, strawberry, raspberry, blueberry, banana, kiwi.

Fresh fruit, dried fruit and canned fruit were considered fruit. Fruit juice was not considered fruit because it has a different food matrix (which may affect the rate of digestion and absorption, and satiation) and it may contain more (added) sugar and less fibre than fresh fruit.

Not all studies report the definition of fruit they used. Therefore, for the current background document, the Committee considered all literature that addressed fruit consumption, despite the definition that was used to determine fruit. This means that, for example, fruit juice may have been considered fruit in some studies.

Vegetables

Vegetables are the edible parts of plants. The Committee followed the EPIC definition of vegetables that was applied for the *Dutch dietary guidelines 2015*[2], which was based on nutrient value, taste and culinary application of plant foods.[3] The following categories of plant foods were considered vegetables (list is not exhaustive):

- Green leaves: spinach, chard, endive, lettuce, watercress, beet leaves;
- Fruit-bearing vegetables: tomatoes, (bell) pepper, avocado, zucchini, cucumber, artichoke, eggplant, pumpkin;
- Tuberous plants: carrots, radish, salsify, beetroot, turnips, celeriac, swede;
- Cabbage crops: broccoli, cabbage, Brussels sprouts, cauliflower;
- Onion and garlic: garlic, onion, shallot, spring onion;

- Stem crops and sprouts: leek, celery, fennel, asparagus, bean sprouts, bamboo shoots;
- Other vegetables: peas, broad beans, corn, mushrooms, button mushrooms, mixed salad, mixed vegetables.

Grains, (sweet) potatoes, legumes, nuts and other tuberous plants were not considered vegetables because of their considerably different nutrient value. Also, vegetable juices were not considered vegetables, because it differs in food matrix and may contain more sugar.

Not all studies report the definition of vegetables they used. Therefore, for the current background document, the Committee considered all literature that addressed vegetables, despite the definition that was used to determine vegetables. This means that, for example, peas and broad beans may have been considered legumes (and not vegetables as in the Committee's definition) in some studies.

1.2 Fruit and vegetable recommendations and intake in the Netherlands

The Health Council of the Netherlands included a guideline for fruit and vegetable consumption in the *Dutch dietary guidelines 2015*, which is as follows[2]: Eat at least 200 grams of vegetables and at least 200 grams of fruit daily.

This guideline is applicable to the general Dutch adult population. The Council has not previously made specific dietary recommendations for people with type 2 diabetes.

Data from the most recent Dutch National Food Consumption Survey (2012-2016) shows that the general Dutch population aged 19 to 79 years consumes on average 112 grams of fruit and 143 grams of vegetables daily.[4]

02 methodology

2.1 Research questions

The Committee aimed to answer the following questions:

1. What is the relationship (effect or association) of fruit consumption with health outcomes in people with type 2 diabetes?
2. What is the relationship (effect or association) of vegetable consumption with health outcomes in people with type 2 diabetes?

The Committee aimed to distinguish between short-term and long-term effects or associations where possible.

2.2 Nutritional topics

The Committee searched for studies into fruit and/or vegetable consumption. Ancillary evidence on the contribution of fruit and vegetable consumption to health outcomes can be obtained from studies into dietary fibre. Specifically, the Committee searched for literature into intakes of dietary fibre from fruit, dietary fibre from vegetables and the fruit-specific dietary fibre *pectin*. The current background document solely focuses on the evidence on fruit and vegetable consumption. The evidence on dietary fibre is described in the background document *Dietary fibre*.[5]

2.3 Outcomes

The Committee selected the following health outcomes for this advisory report (for which a detailed motivation is provided in the background document *Methodology for the evaluation of evidence*[6]):

Surrogate outcomes:

- Glycated haemoglobin (HbA1c);
- Fasting blood glucose;
- Body weight;
- Systolic blood pressure;
- Low-density lipoprotein (LDL) cholesterol;
- Estimated glomerular filtration rate (eGFR).

Long-term health outcomes:

- All-cause mortality;
- Morbidity and/or mortality from total cardiovascular diseases (CVD), coronary heart disease (CHD), stroke, heart failure, chronic obstructive pulmonary disease, total cancer, breast cancer, colorectal cancer, lung cancer, dementia, depression, chronic kidney disease.

Other:

- Diabetes remission: HbA1c <48 mmol/mol and no use of diabetes medication for ≥1 year;
- Diabetes reversion: HbA1c <53 mmol/mol and less medication use for ≥1 year.

For cohort studies, the Committee included only studies with long-term health outcomes.

2.4 Selection and evaluation of literature

A detailed description of the approach used by the Committee for selecting and evaluating scientific literature is provided in the background document *Methodology for the evaluation of evidence*[6]. In short, the Committee aimed to base its evaluation of scientific literature on systematic reviews (SRs), including meta-analyses (MAs), of randomised controlled trials (RCTs) and prospective cohort studies (i.e. prospective cohort studies, nested case-control studies and case-cohort studies) examining the effects or associations of fruit and/or vegetable consumption with the above-mentioned health outcomes in people with type 2 diabetes. In addition, the Committee searched for more recent individual studies that were not included in the most recent SR or MA. The literature search for SRs and MAs was performed in PubMed and Scopus in July 2020. The search strategy, flow diagram of the literature search and detailed description of the study selection are provided in **Annex A**.

2.4.1 Selection of randomised controlled trials

The Committee retrieved two SRs (not MAs) of RCTs on the effect of fruit intake on health outcomes.[7,8] Those SRs examined the effect of a specific type of fruit, i.e. blueberry and cranberry[8] or dragon fruit.[7] Blueberry, cranberry and dragon fruit are only consumed in very small quantities in the Netherlands. Therefore, the Committee considered these SRs not relevant for the Dutch context. No relevant SRs (or MAs) of RCTs on the effect of vegetable consumption were found. As there were no relevant SRs into fruit and vegetable consumption retrieved, the Committee did not conduct an additional search for individual RCTs into fruit and vegetable consumption. So, no RCTs were included in the Committee's evaluation of the effect of fruit and vegetable consumption. This means that there were no studies included that examined effects on the short-term, and no RCTs that examined long-term effects.

2.4.2 Selection of prospective cohort studies

The Committee found no SRs (or MAs) of prospective cohort studies on fruit or vegetable consumption, so deemed it worthwhile to search for individual prospective cohort studies into the relationship between fruit and vegetable consumption with long-term health outcomes in people with type 2 diabetes. The two main reasons were: (1) no RCTs into the effect of

fruit or vegetable consumption on health outcomes were available; (2) no evidence for long-term health outcomes was found via SRs, whereas the Committee was aware of some individual cohort studies that include (large) groups of people with diabetes. The Committee searched for prospective cohort studies in the retrieved SRs and in existing external dietary guidelines for diabetes.[9-14] For the individual studies that were retrieved this way, the committee screened all similar articles and articles citing this study in PubMed.

Two prospective cohort studies were retrieved through screening of external dietary guidelines and citations in PubMed. One of those concerns a pooled analysis of prospective cohorts[15]; the other one concerns an individual cohort study.[16] A third individual cohort study was found via the search for studies into dietary fibre as it examined both fibre intake and fruit and vegetable consumption.[17] In total, one pooled analysis of cohorts and two individual cohort studies were included in the Committee's evaluation[15-17], which addresses associations with all-cause mortality, CVD morbidity and mortality and/or cancer mortality (Table 1). The Committee did not find prospective cohort studies within the pre-specified in- and exclusion criteria for any of the other specified chronic diseases and diabetes remission or reversion.

Table 1 Overview of (pooled analyses of) individual prospective cohort studies selected by the Committee for the evaluation of the association of fruit and/or vegetable consumption with health outcomes.

Dietary exposure	Health outcome[a]	Pooled analysis (of prospective cohort studies)	Prospective cohort studies
Fruit	All-cause mortality	Nöthlings et al., 2008[15]	Du et al., 2017[16]
Fruit	Morbidity or mortality due to CVD	Nöthlings et al., 2008[15]	Du et al., 2017[16]
Fruit	Morbidity due to IHD	None	Du et al., 2017[16]
Fruit	Morbidity due to stroke	None	Du et al., 2017[16]
Fruit	Mortality due to cancer	Nöthlings et al., 2008[15]	None
Vegetables	All-cause mortality	Nöthlings et al., 2008[15]	None
Vegetables	Mortality due to CVD	Nöthlings et al., 2008[15]	None
Vegetables	Mortality due to cancer	Nöthlings et al., 2008[15]	None
Fruit and vegetables	Morbidity or mortality due to CVD	None	Tanaka et al., 2013[17]

CVD: cardiovascular disease; IHD: ischaemic heart disease.

[a] The table contains the health outcomes for which (relevant) studies were found. For the health outcomes that are not listed in the table, no (relevant) studies were found.

2.5 Drawing conclusions

A detailed description of the approach used by the Committee to draw conclusions is provided in the background document *Methodology for the evaluation of evidence*.[6] In short, the Committee drew conclusions on (the certainty of) the evidence regarding the associations of higher fruit and/or vegetable consumption with long-term health outcomes in people with type 2 diabetes, based on the number of studies, number of participants and number of cases that contributed to the evaluation. Also, it took into account the risk of bias and the heterogeneity between studies. The Committee used the decision tree (**Annex B**) as a tool to support consistency in drawing conclusions.

03 associations of fruit and/or vegetable consumption

The scientific evidence for associations of fruit and/or vegetable consumption with long-term health outcomes in people with type 2 diabetes is described in Table 2.

Table 2 Summary of associations of fruit and/or vegetable consumption with risks of all-cause mortality and morbidity or mortality from CVD, CHD, stroke and cancer in people with type 2 diabetes: prospective cohort studies.

Study; Study duration	Nöthlings et al., 2008[15]; 9 years[a]	Tanaka et al., 2013[17]; 8 years[c]	Du et al., 2017[16]; 7 years
Study design	Pooled analysis of 21 cohorts	Individual cohort study	Individual cohort study
Cohort name	EPIC	Japan Diabetes Complications Study	China Kadoorie Biobank Study
Exposure(s)	Fruit consumption, vegetable consumption	Fruit and vegetable consumption	Fruit consumption
Dietary assessment method	Validated country-specific dietary questionnaire at baseline, either quantitative dietary questionnaires with individual portion sizes, or semi-quantitative food frequency questionnaires, or both	Validated food frequency questionnaire on food groups at baseline	Questionnaire at baseline asking for the frequency (daily, 4-6 d/wk, 1-3 d/wk, monthly, rarely/never) of habitual consumption of fresh fruit during the previous 12 mo
Number of participants; number of cases	10449 participants; All-cause mortality: 1346 CVD mortality: 517 Cancer mortality: 319	1414 participants; (Non-)fatal stroke: 68 (Non-)fatal CHD: 96	30300 participants; All-cause mortality: 3389 CVD mortality: 1459 CVD morbidity (non-fatal): 9746 Stroke (non-fatal): 3382 IHD (non-fatal): 3149 Other macrovascular events (non-fatal): 3215
Strength of the association for fruit consumption: HR/RR (95%CI)	Per 80 g/d higher fruit consumption: ALL-CAUSE MORTALITY: 0.95 (0.90-1.01)[b], P-trend=0.42 CVD MORTALITY: 0.90 (0.81-0.99)[b] CANCER MORTALITY: 1.08 (0.98-1.19)[b]	-	Per 1 portion[e]/d higher fruit consumption: ALL-CAUSE MORTALITY: 0.83 (0.74-0.93)[f] CVD MORTALITY: 0.78 (0.65-0.93)[g] CVD MORBIDITY (NON-FATAL): 0.87 (0.82-0.93)[f] STROKE (NON-FATAL): 0.84 (0.76-0.94)[f] IHD (NON-FATAL): 0.92 (0.83-1.02)[f] OTHER MACROVASCULAR EVENTS (NON-FATAL): 0.89 (0.79-1.01)[f]

Study; Study duration	Nöthlings et al., 2008[15]; 9 years[a]	Tanaka et al., 2013[17]; 8 years[c]	Du et al., 2017[16]; 7 years
Strength of the association for vegetable consumption: RR (95%CI)	Per 80 g/d higher vegetable consumption: ALL-CAUSE MORTALITY: 0.87 (0.77-0.97)[b], P-trend 0.03 CVD MORTALITY: 0.85 (0.68-1.07)[b] CANCER MORTALITY: 1.09 (0.87-1.36)[b]	-	-
Strength of the association for fruit and vegetable consumption: HR (95%CI)	-	Per 1 g/d higher fruit and vegetable consumption: (NON-)FATAL STROKE: 0.997 (0.996-0.999)[d], P <0.01 (NON-)FATAL CHD: 1.000 (0.998-1.0001)[d], P 0.82	-
Study population	Participants with self-reported diabetes (type 1 or 2); BMI[a]: 29 ± 5 kg/m^2; diabetes duration: NR; diabetes medication: insulin (21%); men and women; Europe	Participants diagnosed with type 2 diabetes; BMI[a]: 23 ± 3 kg/m^2; diabetes duration: 11 ± 7 y; diabetes medication: oral antihypertensive agents without insulin (65%), insulin (21%); men and women; Japan	Participants with self-reported history of physician-diagnosed diabetes or screen-detected diabetes; BMI[a]: 25 ± 3 kg/m^2; diabetes duration[a,h]: 6 ± 5 y; diabetes medication[g]: oral anti-diabetic agents (62%), insulin (15%), other (23%); men and women; China

BMI: body mass index; CHD: coronary heart disease; CI: confidence interval; CVD: cardiovascular disease; d: days; EPIC: European Prospective Investigation into Cancer and Nutrition; HR: hazard ratio; IHD: ischaemic heart disease; mo: months; NR: not reported; RR: risk ratio; wk: weeks; y: years.

[a] Mean ± standard deviation.

[b] Associations were stratified by age and study centre and adjusted for sex, smoking status, self-reported heart attack at baseline, self-reported hypertension at baseline, self-reported cancer at baseline, waist-to-hip ratio, insulin treatment, aged at diabetes diagnosis, energy intake and alcohol intake.

[c] Median.

[d] Associations were adjusted for age, sex, BMI, HbA1c, diabetes duration, diabetic retinopathy, treatment by insulin, treatment by oral hypoglycaemic agents, systolic blood pressure, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, current smoker, physical activity, alcohol intake, and proportions of total fat, saturated fatty acids, n-6 fatty acids, n-3 fatty acids, dietary cholesterol, sodium intake and energy intake.

[e] One portion equals approximately 100 g.

[f] Associations were stratified by age at risk, sex and region, and were adjusted for education, income, alcohol intake, smoking, physical activity, survey season, BMI, family history of diabetes and intake of dairy products, meat and preserved vegetables.

[g] Associations were stratified by age at risk, sex and region, and were adjusted for education, income, alcohol intake, smoking, physical activity, survey season, BMI, family history of diabetes, intake of dairy products, meat, preserved vegetables, and baseline status of CVD, diabetes and anti-diabetic treatment.

[h] Among participants with previously physician-diagnosed diabetes at baseline (n=16162).

Regarding fruit consumption, the Committee concluded the following:

There is inconclusive evidence regarding the association of fruit consumption with the risk of all-cause mortality in people with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are no MAs of prospective cohort studies that address associations of fruit consumption with risk of all-cause mortality. There is one pooled analysis of 21 cohorts and one (very large) individual cohort study, with in total more than 500 cases of mortality (n=4735), that addresses this topic. This is the first step required to mark the evidence as strong. However, there were other considerations leading to the conclusion of 'inconclusive evidence', as described below.
2. The extent of heterogeneity between the cohort studies contributing to the pooled analysis is unknown. There is no substantial heterogeneity in the direction of the association between the pooled study and the individual study but there is moderate heterogeneity in the size of the association. The pooled analysis showed no statistically significant association between fruit consumption and risk of all-cause mortality, whereas the individual study showed an inverse (beneficial) association. Therefore, the Committee judged that the evidence is inconclusive.

Prospective cohort studies show that a 100 gram higher fruit consumption per day is associated with a 15% lower risk of morbidity or mortality due to CVD in people with type 2 diabetes. The evidence is strong.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are no MAs of prospective cohort studies that address associations of fruit consumption with risks of morbidity or mortality from CVD. There is one pooled analysis of 21 cohorts and one large individual cohort study that addresses this topic, with in total >500 cases. This is the first step required to mark the evidence as strong.
2. The extent of heterogeneity between the cohort studies contributing to the pooled analysis is unknown. The pooled analysis and the individual cohort study both show a beneficial association of higher fruit consumption; there is thus no obvious heterogeneity in direction of the association.
3. There are no other major considerations. This, together with the observation that the result of the pooled analysis is supported by the result of the individual cohort study, led to the judgment of strong evidence.
4. The Committee notes that the conclusion drawn should be viewed in light of the intake range in the evaluated studies, which is approximately 25 to 400 g/d. Whether the observed beneficial association also applies to higher intakes of fruit is unknown.

There is too little research to draw conclusions regarding the association of fruit consumption with the risk of morbidity due to ischaemic heart disease (IHD) in people with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

There are no MAs of prospective cohort studies that address associations of fruit consumption with risk of morbidity due to IHD. There is only one individual prospective cohort study that addresses this association. That is too little evidence to base conclusions on.

There is too little research to draw conclusions regarding the association of fruit consumption with the risk of morbidity due to stroke in people with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

There are no MAs of prospective cohort studies that address associations of fruit consumption with risk of morbidity due to stroke. There is only one individual prospective cohort study that addresses this association. That is too little evidence to base conclusions on.

There is too little research to draw conclusions regarding the association of fruit consumption with the risk of mortality due to cancer in people with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are no MAs of prospective cohort studies that address associations of fruit consumption with risks of cancer mortality. There is one pooled analysis of 21 cohorts, with fewer than 500 cases (n=300), that addresses this topic. This excludes a conclusion with strong evidence, including the conclusion of ‘an association is unlikely’.
2. The pooled analysis shows no association between fruit consumption and risk of cancer mortality. The extent of heterogeneity between the cohort studies contributing to the pooled analysis is unknown. All cohorts in this pooled analysis are from the same consortium (EPIC) and thus any dependency between cohorts cannot be ruled out (meaning the level of evidence can be at most ‘limited’). Since there is no other study that supports the result of the pooled analysis, evidence was considered limited and thus was not sufficient to conclude that an association is unlikely. Therefore, the Committee downgraded its conclusion and concluded that there is too little research.

Regarding vegetable consumption, the Committee concluded the following:

Prospective cohort studies show that higher vegetable consumption is associated with a lower risk of all-cause mortality in people with type 2 diabetes. The evidence is limited.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are no MAs of prospective cohort studies that address associations of vegetable consumption with risk of all-cause mortality. There is one pooled analysis of 21 cohorts, with more than 500 cases of mortality (n=1346), that addresses this topic. This is the first step required to mark the evidence as strong. However, there were other considerations leading to the conclusion with limited evidence, as described below.
2. The pooled analysis shows an inverse (beneficial) association between vegetable consumption and risk of all-cause mortality. The extent of heterogeneity between the cohort studies contributing to the pooled analysis is unknown. All cohorts in this pooled analysis are from the same consortium (EPIC) and thus any dependency between cohorts cannot be ruled out. Since there was no other study that supports the results of the pooled analysis, the Committee judged the evidence as limited.

There is too little research to draw conclusions regarding the association of vegetable consumption with the risk of mortality due to CVD in people with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are no MAs of prospective cohort studies that address associations of vegetable consumption with risk of CVD mortality. There is one pooled analysis of 21 cohorts, with more than 500 cases, that addresses this topic. This is the first step required to mark the evidence as strong. However, there were other considerations leading to the conclusion of ‘too little research’, as described below.
2. The pooled analysis shows no association between vegetable consumption and risk of CVD mortality. The extent of heterogeneity between the cohort studies contributing to the pooled analysis is unknown. All cohorts in this pooled analysis are from the same consortium (EPIC) and thus any dependency between cohorts cannot be ruled out (meaning the level of evidence can be at most ‘limited’). Because there is no other study that supports the result of the pooled analysis, evidence was considered limited and thus was not sufficient to conclude that an association is unlikely. Therefore, the Committee downgraded its conclusion and concluded that there is too little research.

There is too little research to draw conclusions regarding the association of vegetable consumption with the risk of mortality due to cancer in people with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

1. There are no MAs of prospective cohort studies that address associations of vegetable consumption with risk of cancer mortality. There is one pooled analysis of 21 cohorts, with fewer than 500 cases (n=300), that addresses this topic. This excludes a conclusion with strong evidence, including the conclusion of ‘an association is unlikely’.
2. The pooled analysis shows no association between vegetable consumption and risk of cancer mortality. The extent of heterogeneity between the cohort studies contributing to the pooled analysis is unknown. All cohorts in this pooled analysis are from the same consortium (EPIC) and thus any dependency between cohorts cannot be ruled out (meaning the level of evidence can be at most ‘limited’). Because there is no other study that supports the result of the pooled analysis, evidence was considered limited and thus was not sufficient to conclude that an association is unlikely. Therefore, the Committee downgraded its conclusion and concluded that there is too little research.

Regarding fruit and vegetable consumption combined, the committee concluded the following:

There is too little research to draw conclusions regarding the association of fruit and vegetable consumption combined with the risk of morbidity or mortality due to CVD in people with type 2 diabetes.

The following considerations were made by the Committee, following the steps of the decision tree, to come to this conclusion:

There are no MAs of prospective cohort studies that address associations of fruit and vegetable consumption combined with risk of morbidity or mortality from CVD. There is only one individual prospective cohort study that addresses this association. That is too little evidence to base conclusions on.

Explanation:

The study by **Nöthlings et al.**[15] is a pooled analysis of 21 cohorts from the European Prospective Investigation into Cancer and Nutrition (EPIC) study, covering nine European countries. It aimed, among others, to examine the association of fruit and vegetable consumption with risks of all-cause and cause-specific mortality in people with diabetes. A total of 10449 men and women with self-reported diabetes (type 1 and type 2) at baseline were included. Mean follow-up time was 9 years (range: 1 to 14

years), during which 1346 cases of mortality were reported, of which 517 cases were due to CVD and 319 were due to cancer.

Median fruit consumption was 130, 195, 262 and 379 g/d in quartiles 1 to 4, respectively, and median vegetable consumption was 127, 164, 198 and 259 g/d. Most likely, fruit concerned not only fresh fruit. In the total EPIC cohort (diabetics and non-diabetics), fruit concerned mostly (>90%) fresh fruit, but also canned and dried fruit. It did not include fruit juices.[19] Regarding fruit consumption, this pooled study showed no association between fruit consumption and risk of all-cause mortality (HR per 80 g/d higher fruit consumption 0.95, 95%CI 0.90-1.01). However, when fruit intake was categorically analysed, a statistically significant beneficial association was observed with the risk of all-cause mortality for quartile 2 compared to quartile 1 (HR 0.83, 95%CI 0.71-0.98), but not for quartiles 3 and 4. The authors provided no explanation for this. With respect to cause-specific mortality, each 80 g/d higher consumption of fruit was statistically significantly associated with a 10% lower risk of CVD mortality (HR 0.90, 95%CI 0.81-0.99) but not with cancer mortality (HR 1.08, 95%CI 0.98-1.09). Regarding vegetable consumption, this study showed that each 80 g/d higher consumption of vegetables was associated with a lower risk of all-cause mortality (HR 0.87, 95%CI 0.77-0.97) but not with the risks of CVD mortality (HR 0.85, 95%CI 0.68-1.07) or cancer mortality (HR 1.09, 95%CI 0.87-1.36).

Self-reported diabetes could be either type 1 or type 2 diabetes. The authors attempted to exclude participants with type 1 diabetes by performing sensitivity analyses in participants being diagnosed with diabetes at age 40 or older (n=4901) or those reporting not to use insulin (n=4809). Those sensitivity analyses were only performed with the exposure being a combination of fruit consumption, vegetable consumption and legume consumption, and only for the outcome of all-cause mortality. The observed association in those diagnosed with diabetes age 40 or older was essentially the same as in the total study population, suggesting no effect modification by type of diabetes. The subgroup analysis based on insulin treatment (yes/no) showed a stronger (P<0.0001) association of fruit, vegetable and legume consumption with all-cause mortality in participants without insulin treatment (n=6555) compared to those with insulin treatment (n=2197). It is most likely that the group of non-insulin users comprised of people with type 2 diabetes only. Based on those analyses, the Committee judged that the overall results from this study (based on people with type 1 and type 2 diabetes) likely also apply to people with type 2 diabetes and therefore considered those results relevant for this advisory report.

Tanaka et al.[17] aimed to examine the association of fruit and/or vegetable consumption (combined) with risks of (non-)fatal stroke and CHD in participants diagnosed with type 2 diabetes (HbA1c ≥6.5%). This prospective cohort study included 1414 Japanese men and women from

the Japanese Diabetes Complications Study who had diabetes at baseline. Baseline age ranged from 40 to 70 years. Median follow-up time was 8 years, during which 68 cases of stroke and 96 cases of CHD occurred.

Mean (± SD) consumption of fruit and vegetables ranged from 229 ± 84 g/d in quartile 1 to 721 ± 197 g/d in quartile 4. The definitions of fruit and vegetables are lacking, so it is unclear if these food groups reflect only fresh fruits and vegetables or that also canned and dried products are included. The study showed that higher fruit and/or vegetable consumption (combined) was statistically significantly associated with a lower risk of (non-)fatal stroke (HR per +1 g/d 0.997, 95%CI 0.996-0.999; P<0.01), but not with the risk of (non-)fatal CHD (HR per +1 g/d 1.000, 95%CI 0.998-1.001; P 0.82). Associations were adjusted for a range of covariates including body mass index (BMI) and energy intake. When analysed categorically, compared to quartile 1 of fruit and/or vegetable consumption (mean ± SD 229 ± 84 g/d), no association was observed with the risk of stroke for quartile 2 (372 ± 83 g/d; HR 0.72, 95%CI 0.36-1.44) but a lower risk of stroke was observed for quartile 3 (499 ± 94 g/d; HR 0.45, 95%CI 0.19-1.04) and quartile 4 (721 ± 197 g/d; HR 0.35, 95%CI 0.13-0.96). No associations were observed of quartiles of fruit and/or vegetable consumption with CHD risk.

Du et al.[16] examined the association between fresh fruit consumption and risks of all-cause mortality, cause-specific mortality and hospitalization due to cardiovascular complications in people with diabetes. This prospective cohort study included 30300 Chinese men and women from the China Kadoorie Biobank study who had diabetes at baseline. Baseline age ranged from 35 to 74 years. Participants had either self-reported or screen-detected diabetes. Self-reported diabetes means a prior history of physician-diagnosed diabetes. Screen-detected diabetes was assessed in participants with no self-reported diabetes and defined as never being diagnosed with diabetes but having a random blood glucose between ≥7.0 mmol/L with time since last food/beverage consumption ≥8 hours or ≥11.1 mmol/L with time since last food consumption <8 hours, or a fasting blood glucose level of ≥7.0 mmol/L. The authors estimated that 0.2% of the people with diabetes had type 1 diabetes, based on diagnosis at age <30 years and insulin use. The authors did not perform a subgroup or sensitivity analysis excluding these participants. It remains unknown whether these participants who potentially have type 1 diabetes had influenced the results, but given the very small proportion the impact is expected to be marginal. Mean follow-up time was 7 years, during which 3389 cases of all-cause mortality were reported (of which 1459 due to CVD) and 9746 cases of non-fatal CVD (of which 1459 due to stroke and 3382 due to IHD).

Mean fresh fruit consumption generally ranged from 25 to 125 g/d. The study showed that each additional daily portion of fruit (equals approximately 100 g/d) was statistically significantly associated with a

17% lower risk of all-cause mortality (HR 0.83, 95%CI 0.74-0.93), a 22% lower risk of CVD mortality (HR 0.78, 95%CI: 0.65-0.93) and a 13% lower risk of CVD morbidity (HR 0.87, 95%CI 0.82-0.93). The association was a little stronger for risk of morbidity due to stroke (HR 0.84, 95%CI 0.76-0.94) than for risk of morbidity due to IHD (HR 0.92, 95%CI 0.83-1.02). The type of anti-diabetic treatment (i.e. oral drugs, insulin, no treatment or other) and the age of diabetes onset (<45, 45-55, 55-65 or ≥65 years) did not substantially modify the strength of the association. Associations were not adjusted for total energy intake, but they were adjusted for BMI and physical activity level (and multiple other covariates).

Funding or author's conflicts of interest likely did not affect the study findings of the studies included in this evaluation (**Annex C**).

04 summary of conclusions

The Committee's conclusions regarding associations of fruit and/or vegetable consumption with health outcomes in people with type 2 diabetes are summarised in Table 3.

Table 3 Overview of conclusions regarding the associations of fruit and/or vegetable consumption with health outcomes in people with type 2 diabetes, based on prospective cohort studies.

Dietary exposure	Health outcome[a]	Conclusion
Fruit	All-cause mortality	Inconclusive evidence
Fruit	Morbidity or mortality due to CVD	Strong evidence for an inverse association
Fruit	Morbidity due to IHD	Too little research
Fruit	Morbidity due to stroke	Too little research
Fruit	Mortality due to cancer	Too little research
Vegetables	All-cause mortality	Limited evidence for an inverse association
Vegetables	Mortality due to CVD	Too little research
Vegetables	Mortality due to cancer	Too little research
Fruit and vegetables	Morbidity or mortality due to CVD	Too little research

CVD: cardiovascular disease; IHD: ischaemic heart disease.

[a] The table contains the health outcomes for which (relevant) studies were found. For the health outcomes that are not listed in the table, no (relevant) studies were found.

references

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annex A
search strategy, study selection and flow diagram

Systematic reviews including meta-analyses

The Committee performed a literature search to identify relevant systematic reviews (SRs) including meta-analyses (MAs) on the relationship between carbohydrate-containing food sources and health outcomes in people with type 2 diabetes. Literature searches were performed in PubMed and Scopus on 20th and 29th July 2020, respectively, using the following search strategies:

PubMed

(“diabetes mellitus, type 2”[MeSH] OR Diabet*[tiab] OR T2DM[tiab] OR NIDDM[tiab]) AND ((“Dietary Fiber”[Mesh] OR “Dietary Carbohydrates”[Mesh] OR “Starch”[Mesh] OR “Polysaccharides”[Mesh] OR “Fructans”[Mesh] OR “Inulin”[Mesh] OR “Dietary sugars”[Mesh] OR (dietary[tiab] AND (fiber*[tiab] OR fibre*[tiab] OR carbohydrates[tiab] OR starch*[tiab] OR fructan[tiab] OR inulin[tiab] OR sugar*[tiab]))) OR ((“edible grain”[MeSH] OR “edible grain”[tiab] OR cereals[tiab] OR “Whole Grains”[Mesh] OR grain*[tiab] OR wheat*[tiab] OR oat[tiab]) OR (fruit[MeSH] OR fruit[tiab] OR fruits[tiab]) OR (vegetables[MeSH] OR vegetables[tiab]) OR (((sugars[MeSH] OR sugars[tiab] OR sugar[tiab] OR sweetened[tiab] OR sweetener[tiab]) AND (beverages[MeSH] OR beverages[tiab] OR drink*[tiab] OR juice*[tiab] OR soda*[tiab]))) OR (fabaceae[MeSH] OR fabaceae[tiab] OR legume[tiab] OR legumes[tiab] OR bean*[tiab] OR “Soybean Proteins”[Mesh]OR soy[tiab] OR soya[tiab]))) AND (Systematic review[publication type] OR Meta-analysis[publication type] OR review[tiab] OR “meta-analysis”[tiab] OR meta analysis[tiab] OR metaanalysis[tiab] OR quantitative review[tiab] OR quantitative overview[tiab] OR systematic review[tiab] OR systematic overview[tiab] OR methodologic review[tiab] OR methodologic overview[tiab])

Limit: from 2000 + English

Scopus

(((KEY (“diabetes mellitus, type 2”) OR TITLE-ABS-KEY (t2dm) OR TITLE-ABS-KEY (niddm))) OR (TITLE-ABS (“diabetes mellitus, type 2”) OR TITLE-ABS (diabet*) OR TITLE-ABS (t2dm) OR TITLE-ABS (niddm))) AND ((((TITLE-ABS-KEY (“Dietary Fiber”) OR TITLE-ABS-KEY (“Dietary Carbohydrates”) OR TITLE-ABS-KEY (“Starch”) OR TITLE-ABS-KEY (“Polysaccharides”) OR TITLE-ABS-KEY (“Fructans”) OR TITLE-ABS-KEY (“Inulin”))) OR ((TITLE-ABS (dietary)) AND (TITLE-ABS (fiber*) OR TITLE-ABS (fibre*) OR TITLE-ABS (carbohydrates) OR TITLE-ABS (starch*) OR TITLE-ABS (fructan) OR

TITLE-ABS (inulin) OR TITLE-ABS (sugar)))) OR ((TITLE-ABS-KEY (“edible grain”)) OR ((TITLE-ABS-KEY (cereals) OR KEY (“Whole Grains”) OR TITLE (grain*) OR ABS (grain*) OR TITLE (wheat*) OR ABS (wheat*) OR TITLE (oat) OR ABS (oat))) OR (KEY (fruit) OR TITLE-ABS (fruit) OR TITLE-ABS (fruits)) OR (KEY (vegetables) OR TITLE-ABS (vegetables)) OR (KEY (sugars) OR TITLE-ABS (sugar) OR TITLE-ABS (sugars) OR TITLE-ABS (sweetened) OR TITLE-ABS (sweetener) OR KEY (beverages) OR TITLE-ABS (beverages) OR TITLE-ABS (drink*) OR TITLE-ABS (juice*) OR TITLE-ABS (soda*) OR KEY (fabaceae) OR TITLE-ABS (fabaceae) OR TITLE-ABS (legume) OR TITLE-ABS (legumes) OR KEY (“Soybean Proteins”) OR TITLE-ABS (soy) OR TITLE-ABS (soya)))) AND (((TITLE-ABS-KEY (“Systematic review”) OR TITLE-ABS-KEY (“Meta-analysis”))) OR (TITLE-ABS (review) OR TITLE-ABS (meta-analysis) OR TITLE-ABS (meta analysis) OR TITLE-ABS (“quantitative review”) OR TITLE-ABS (“quantitative overview”) OR TITLE-ABS (“systematic overview”) OR TITLE-ABS (“methodologic review”) OR TITLE-ABS (“methodologic overview”)))

Limit: from 2000 + English

In total, 2054 publications were found in PubMed and 3887 publications in Scopus. After removal of duplicates, 4527 publications remained and were screened for title and abstract. A total of 172 publications remained for full-text assessment, of which 19 were selected for the Committee’s evaluation of high-carbohydrate foods.

Of those 19 publications, 2 publications on fruit and/or vegetable consumption fulfilled the Committee’s criteria. However, those SRs concerned very specific types of fruit, i.e. dragon fruit[7] or blueberry and cranberry.[8] Since these fruits are only consumed in very small quantities in the Netherlands, the Committee judged that those SRs were not relevant for the Dutch context. No SRs remained for the Committee’s evaluation of fruit and vegetable consumption.

Prospective cohort studies

Since no SRs or MAs of (multiple) cohort studies were found, the Committee searched for individual prospective cohort studies on associations of fruit and/or vegetable consumption with long-term health outcomes in the retrieved SRs and in external dietary guidelines for diabetes of the following organisations:

- Dutch Diabetes Federation (Nederlandse Diabetes Federatie (NDF)), 2020[9]
- European Association for the Study of Diabetes (EASD) & European Society of Cardiology (ESC), 2020[10]

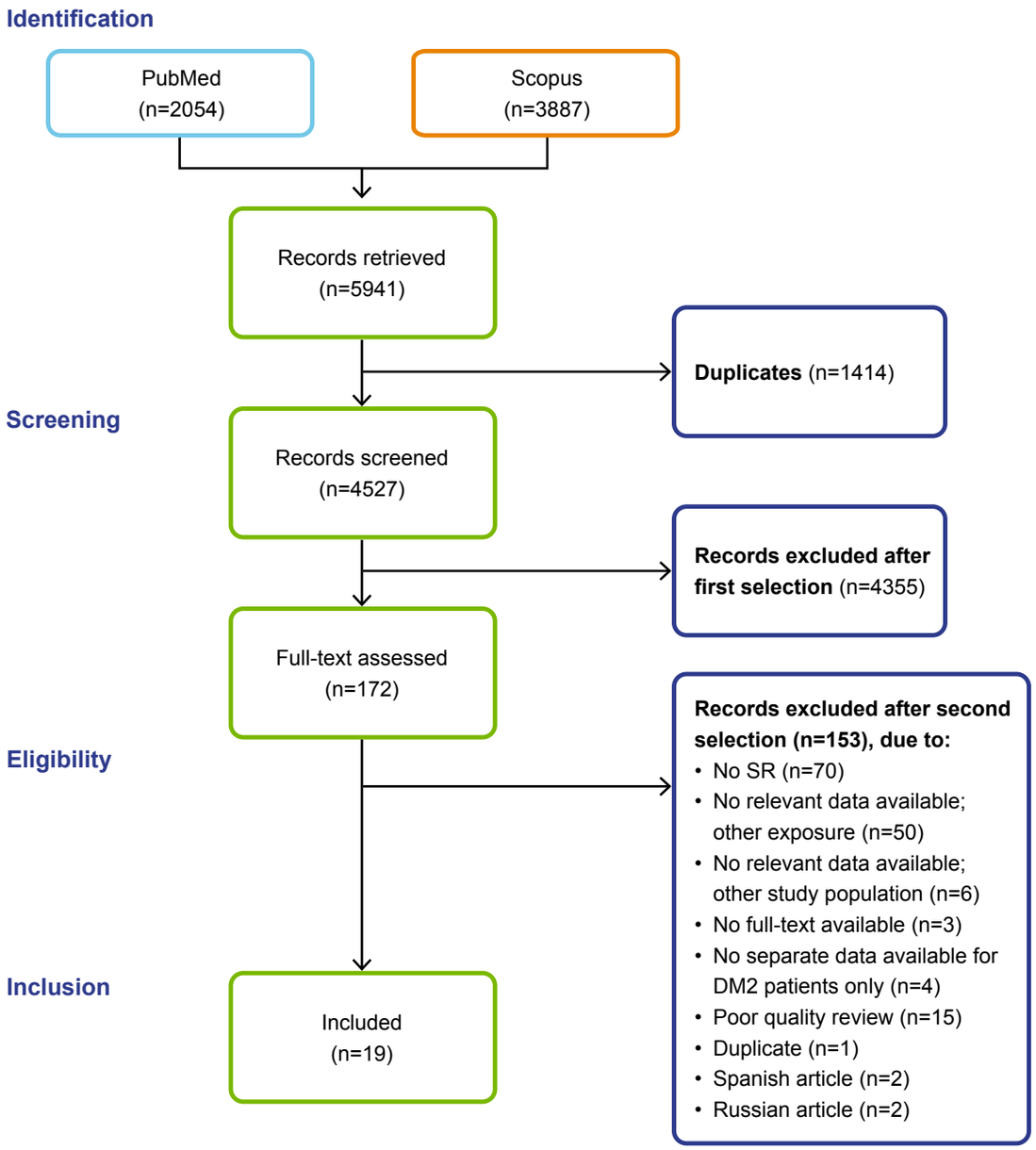
- American Diabetes Association (ADA), 2019[11]
- Diabetes UK, 2018[12]
- Diabetes Canada, 2018[13]
- Swedish Council, 2010[14]

One pooled analysis of prospective cohorts[15] was retrieved through screening of the dietary guidelines for diabetes of the Swedish Council[14]. Subsequently, articles citing this study were searched in PubMed. This yielded one additional relevant (individual) cohort study.[16] The search for studies on dietary fibre yielded one (individual) cohort study that – in addition to fibre intake – also examined fruit and vegetable consumption in relation to health outcomes.[17] Screening of SRs yielded no additional relevant studies.

The Committee selected the following pooled analysis of prospective cohorts and individual prospective cohort studies for its evaluation of fruit and/or vegetable consumption:

- Nöthlings et al., 2008[15] (pooled analysis of prospective cohort studies)
- Du et al., 2017[16]
- Tanaka et al., 2013[17]

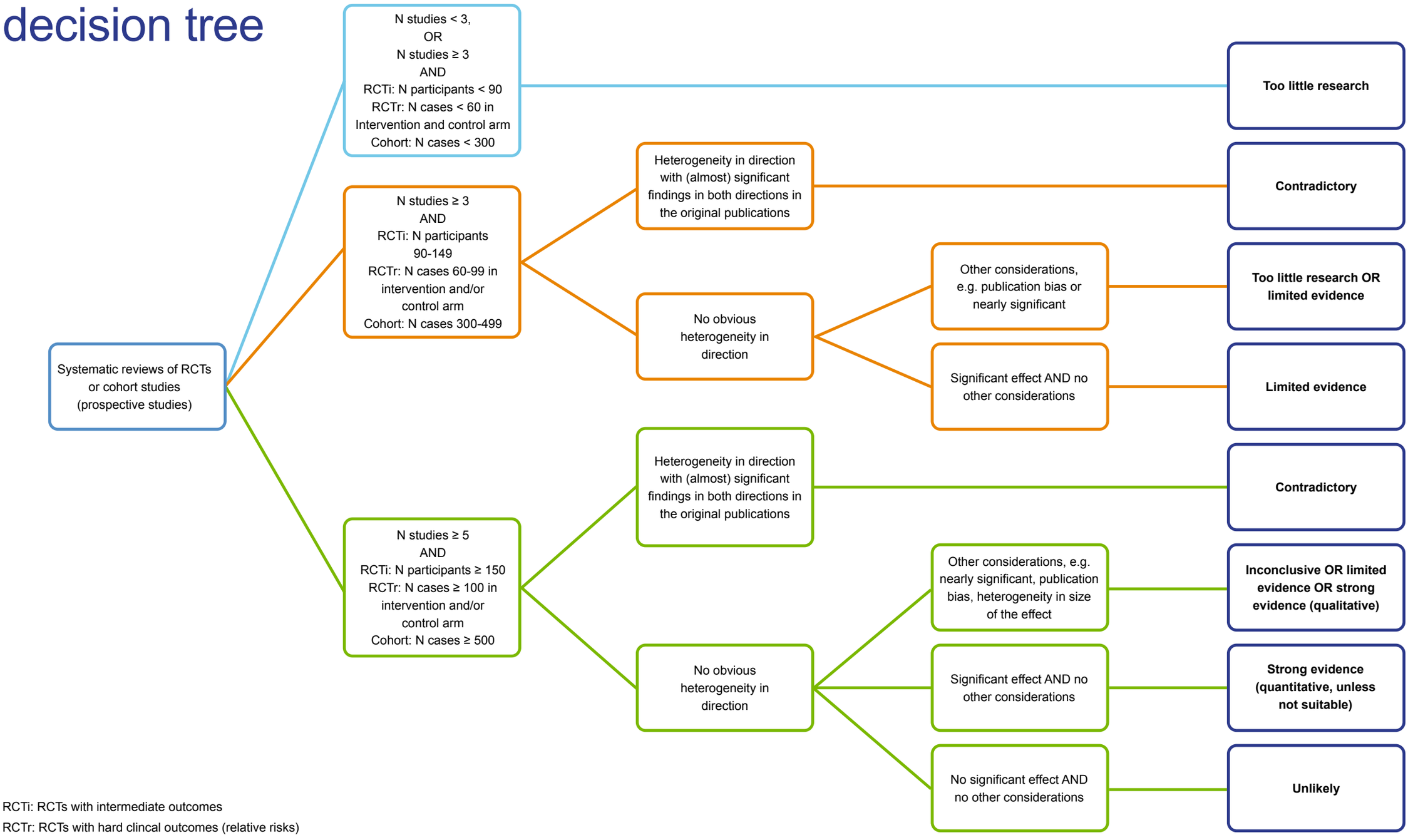
Flow diagram for the selection of systematic reviews including meta-analyses



DM2: type 2 diabetes.

annex B

decision tree



RCTi: RCTs with intermediate outcomes

RCTr: RCTs with hard clincal outcomes (relative risks)

annex C

funding sources and conflicts of interest regarding the articles used in this background document

In the table below, the funding sources of the studies listed in this background document and conflicts of interests of authors contributing to those studies are reported.

Study's first author, year	Funding of the work	Conflicts of interest of authors
Du, 2017[16]	The study (surveys) was supported the Kadoorie Charitable Foundation (China) and the UK Wellcome Trust, the Chinese Ministry of Science and Technology and the Chinese National Natural Science Foundation. The Clinical Trial Service Unit (University of Oxford) was funded by the British Heart Foundation, the Medical Research Council and the Cancer Research UK.	One author received support from the British Heart Foundation Centre of Research Excellence (Oxford). One author was a member of the Editorial Board of PLOS Medicine. The other authors declared to have no conflicts of interest.
Nöthlings, 2008[154]	The study was supported by the Community (Directorate-General SANCO: Directorate X-Public Health and Risk Assessment). Financial support for the EPIC study came from the European Commission, national ministries (e.g. Spanish Ministry of Health, Greek Ministry of Education and Dutch Ministry of Public Health, Welfare and Sports) and research councils (e.g. Medical research Council UK, Italian Association for Research on Cancer and Danish Cancer Society).	The authors declared to have no conflicts of interests.
Tanaka, 2013[17]	The study was financially supported by the Ministry of Health, Labour and Welfare of Japan.	The authors declared to have no conflicts of interests.

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues and health (services) research...” (Section 22, Health Act).
The Health Council receives most requests for advice from the Ministers of Health, Welfare and Sport, Infrastructure and Water Management, Social Affairs and Employment, and Agriculture, Nature and Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.
Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity.
The reports are available to the public.

This publication can be downloaded from www.healthcouncil.nl.

Preferred citation:
Health Council of the Netherlands. Fruit and vegetables. Background document to Dutch dietary guidelines for people with type 2 diabetes.
The Hague: Health Council of the Netherlands, 2021; publication no. 2021/41Be.